REMARKS

Claims 1-3 are pending in the application. Claims 1-3 are amended. No new matter is added by these amendments.

Reconsideration is respectfully requested in view of the above amendments and following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

Sequence Information

Applicant submits herewith Sequence Listings of nucleotide sequences disclosed in this application in accordance with 37 C.F.R. §§ 1.821-1.825. The Specification is amended on pages 7, 11-12, and 18 (Table 1) to conform with the requirements of Sequence disclosures.

Oath/Declaration

Applicant submits herewith a new Declaration in compliance with 37 C.F.R. 1.67(a).

Priority

Applicant amends the Specification on page 1 to specify that the filing date of the parent U.S. application 09/142,779 was April 13, 1999, as correctly noted by the Examiner.

Rejections Under 35 U.S.C. § 112, second paragraph

(i) Claims 2-3 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness.

Applicant amends dependent claims 2 and 3 to recite "[t]he method of claim 1" in the preamble according to established practice. Applicant respectfully requests that the objection to these claims as vague and indefinite on these grounds, be withdrawn.

(ii) Claim 3 stands rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness.

The Examiner objects to the Markush group listing of "vascular cells, smooth muscle cells, endothelial cells and neoplasia cells" on the grounds that "all members of the Markush group read on some form of vascular cell."

Applicant respectfully traverses the Examiner's interpretation that the Specification describes neoplasia cells as a species of vascular cells. Page 4, lines 20-21 recites: "*the cells* are vascular cells, particularly smooth muscle or endothelial cells." (emphasis added). The *next*

sentence recites: "*[t]he cells may*, however, be cells involved in neoplasia." (emphasis added). This reference to neoplasia cells in the Specification does not describe them as a sub-species of vascular cells, but describe the cells as an alternative embodiment of cells whose proliferation may be inhibited by the screened compounds.

Applicant amends independent claim 1 to specify "compounds which inhibit proliferation of cells selected from the group consisting of vascular cells and neoplasia cells." Applicant also amends dependent claim 3 to specify the limitation "wherein the vascular cells are selected from the group consisting of smooth muscle cells and endothelial cells." Applicants submit that, in view of these amendments, "smooth muscle cells and endothelial cells" are properly claimed in dependent claim 3 as limitations on the "vascular cells" specified in independent claim 1. Neoplasia cells are properly claimed as a separate Markush group embodiment in independent claim 1, in accordance with the description provided in the Specification.

Rejections Under 35 U.S.C. § 102

(i) Claims 1-3 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Muthukkumar et al. Applicant respectfully traverses this rejection.

The claims of the instant application are based on the finding that Egr-1 stimulates proliferation of cells such as vascular cells and neoplasia cells, and agents such as Egr-1 antisense oligonucleotides successfully block this proliferative activity. The claims are directed to screening for compounds that "**inhibit proliferation of cells** selected from the group consisting of vascular cells and neoplasia cells" (emphasis added) by inhibition of Egr-1.

In contrast, Muthukkumar *et al.* assert that Egr-1 mediates an **anti-proliferative** (Muthukkumar et al., *Mol. Cell. Biol.* 15(11):6262-6272 (1995), *see* Figure 9 and page 6269) and **pro-apoptotic** (*id.,* Figure 10 and page 6269) influence on cancer cells. The Examiner notes that according to Muthukkumar et al. phosphorothioate-modified antisense oligonucleotides targeting human Egr-1 mRNA inhibit thapsigargin (TG)-inducible expression of EGR-1 (*id.,* Figure 8 and page 6268). However, administration of the compounds (antisense oligonucleotides) according to Muthukkumar et al. *reduces* TG-induced *growth inhibition* (*id.,* Figure 9 and page 6269) and

inhibits TG-induced *apoptosis* (cell death) (*id.*, Figure 10 and page 6269). Thus, Muthukkumar et al. teach that inhibition of Egr-1 expression **promotes** cell proliferation. Accordingly, Muthukkumar et al. **teach away** from a method of **inhibiting the proliferation** of cells which involves reducing EGR-1 activity.

Therefore, Applicant submits that the Muthukkumar reference does not anticipate each and every element of the claimed invention. Applicant respectfully requests withdrawal of these grounds for rejection.

(ii) Claims 1-3 stand rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Hu, *et al.*

The Hu reference is cited for disclosing the use of Tis 8 (Egr-1 gene) antisense oligonucleotides to inhibit expression of the Egr-1 gene in astrocytes. The reference deals exclusively with the growth of central nervous system (astrocyte) cells, and the observations made by Hu, *et al.* relate specifically to modulation of astrocyte proliferation. The reference does not teach or suggest that down-regulation of the Egr-1 gene activity would inhibit proliferation of any other cell types. To draw any inference from Hu, *et al.* that inhibition of Egr-1 gene would also inhibit proliferation of vascular, such as smooth muscle and endothelial cells, or neoplasia cells, as instantly claimed, is highly speculative and has no basis in the cited art.

Therefore, Applicant submits that the Hu, *et al.* reference does not anticipate each and every element of the claims as amended. Withdrawal of the rejection on these grounds is respectfully requested.

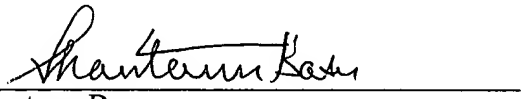
Conclusion

In light of the Amendments and the arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 273402002020.

Respectfully submitted,

Dated: January 31, 2002 By: 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

This application is a continuation-in-part of U.S. Serial No. 09/142,779, filed [September 8, 1998] April 13, 1999 and which issued as U.S. Pat. No. 6,200,960 B1 on March 13, 2001, which is a 371 of PCT/AU97/00140, filed March 7, 1997, which claims priority to Australian PN 8554, filed March 7, 1996, the disclosures of each of which are incorporated herein by reference in their entirety.

Please replace the paragraph on page 7, starting at line 11 with the following:

In a second aspect the present invention consists in an oligonucleotide for use in decreasing biosynthesis of Egr-1, the oligonucleotide having the sequence ACA CTT TTG TCT GCT (SEQ ID No:1).

Please replace the paragraph on pages 11 and 12, starting at line 26 with the following:

In response to mechanical injury in vitro, confluent endothelial cells initiate movement into the open "wounded" area by actively responding to locally-derived signals or autocoids from injured cells. An in vitro model of vascular injury (L. Muthukrishnan, E. Warder, P.L. McNeil, *J. Cell. Physiol.* 148, 1-16 (1991)) was used to address the possible link between Egr-1 and injury-induced PDGF-B gene expression. Nuclear run-off analysis revealed that Egr-1 gene transcription was induced in cultured bovine aortic endothelial cells (BAEC) within 1 h of injury. 5' deletion analysis of the PDGF-B promoter in endothelial cells previously defined a region necessary for core promoter activity (d77) which contained a binding site for the ubiquitous transcription factor, Sp1 (L.M. Khachigian, J.W.U. Fries, M.W. Benz, D.T. Bonthron, T. Collins, *J. Biol. Chem.* 269, 22647 (1994)). Recent in vivo footprint analysis of the promoter demonstrates that the Sp1 element is indeed occupied in intact cells (R.P.H. Dirks, H.J. Jansen, B. van Gervan, C. Onnekink, H.P.J. Bloemers, *Nucleic Acids Res.* 23, 1119 (1995)). In vitro DNase I footprinting revealed that recombinant Egr-1 protected a region overlapping this site from partial DNase I digestion. When nuclear extracts from endothelial cells 1h after injury

were incubated with a ^{32}P-labelled oligonucleotide spanning this region (^{32}P-Oligo B, 5'-GCTGTCTCCACCCACCTCTCGCACTCT-3') (SEQ ID No:2), a distinct nucleoprotein complex formed. The injury-induced complex was eliminated by antibodies to Egr-1. Nuclear Sp1 also bound to the PDGF-B promoter fragment; however, its levels are unaltered by injury. Thus, injury-induced endothelial Egr-1 expression precedes the induction of PDGF-B, and Egr-1 binds to a distinct region in the PDGF-B promoter also bound by Sp1.

Please replace Table 1 on page 18 with the following:

Table 1. Nucleotide Sequence of Oligonucleotides (5' –>3')

E1	CGC	CAT	TAC	CTA	GTG (SEQ ID NO: 3)
A/S2	CTT	GGC	CGC	TGC	CAT (SEQ ID NO: 4)
E6	CCA	GGC	TGG	CGG	TAG (SEQ ID NO: 5)
E7	GAG	AAC	TGA	TGT	TGG (SEQ ID NO: 6)
E9	TGT	GGT	CAG	GTG	CTC (SEQ ID NO: 7)
E11	ACA	CTT	TTG	TCT	GCT (SEQ ID NO: 8)

In the Claims:

1. (Amended) A method of screening for compounds which inhibit [the] proliferation of cells selected from the group consisting of vascular cells and neoplasia cells, the method comprising determining the ability of a putative compound to inhibit induction of Egr-1, decrease expression of Egr-1 or decrease the nuclear accumulation or activity of the Egr-1 gene product.

2. (Amended) [A]The method [as claimed in]of claim 1, wherein the method is performed *in vitro*.

3. (Amended) [A]The method [as claimed in]of claim 1 or claim 2, wherein the vascular cells are selected from the group consisting of [vascular cells,]smooth muscle cells[,] and endothelial cells[and neoplasia cells].